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COMPARATIVE RISK ASSESSMENT OF CROSS-SENSITIZATION TO METHACRYLIC MONOMERS IN DENTAL PRACTICE

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ABSTRACT

Background: Methacrylates serve as a base for resin-based dental materials, extensively used in practice. They may cause irritation to skin, eyes, and mucous membranes, allergic dermatitis, stomatitis, etc. Acrylic monomers often cross-react. Numerous studies confirm the sensitization to methacrylates in dental professionals, but quite a few evaluate the incidence of cross-sensitization in students of dentistry and from dental technician school. The purpose of the present study is to perform a comparative risk assessment of cross-sensitization to methacrylates in different groups of individuals, exposed in dental practice.

Materials and methods: A total of 262 participants were included: dental professionals, students of dentistry and from dental technician school and dental patients. All of them were patch-tested with methacrylic monomers, included in DMS-1000 series. The results were subject to statistical analysis ($p < 0.05$).

Results: High sensitization rates were revealed, with highest cross-sensitization incidence in the groups of dental patients and the students of dentistry. The most common methacrylic allergens for dental professionals were 2-HEMA and TEGDMA, for students of dentistry - TEGDMA, bis-GMA and 2-HEMA, for students of dental technician school – TEGDMA and MMA, and for control group - bis-GMA and THFDMA. Students of dentistry and the control group could be considered at risk of cross-sensitization to methacrylic monomers.

Conclusions: We assume a significant role of therapy with composite materials for the sensitization to methacrylates. More effective training and risk management programs in exposure to allergens and use of proper personal protection in dental practice and among dental students could be recommended.

INTRODUCTION

Dental material contains a number of allergens and irritants that may give rise to health issues for patients to which they have been applied as well as for dental students during their education (Atai Z. and Atai M., 2007, Kanerva et al, 1994). Methacrylates serve as a base for acrylic resins (Mikov, 2011). Resin-based dental materials are extensively used today in dentistry. Examples of include general dental applications dentures (bases, liners, tissue conditioners, artificial teeth, temporary restoration, etc.), cavity restorative materials (composites – self / light curing), pulpal, cavity and margin sealants, impression materials (alginate, agar, elastomers, waxes, etc.), resin based cements, dentin bonding agents, orthodontic appliances, habit breaking appliances (nail biting, thumb sucking, etc.), oral and maxillofacial appliances, cleft palate plates maxillary supports, etc. (Gosavi, 2010). Acrylic resin dentures contain methyl methacrylate (MMA) as residual monomer (Keyf, 1998). The most frequently occurring methacrylates in bonding materials are 2-hydroxy-ethyl methacrylate (2-HEMA) and 2,2-bis-[4-(2-hydroxy-3-methacrylo-xypropoxy)phenyl]-propane (bis-GMA). Bis-GMA and triethyleneglycol dimethacrylate (TEGDMA) are the most frequently occurring methacrylates in composite resins. The main methacrylate of the glass ionomers is 2-

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HEMA (Henriks-Eckerman, 2004). Completely polymerized, acrylic plastics are inert and harmless. Cured methacrylates also can volatilize, thereby causing respiratory irritation and sensitization and allergic symptoms (Sasseville, 2012). Experimental and clinical studies have documented that methacrylic monomers may cause a wide range of adverse health effects such as irritation to skin, eyes, and mucous membranes, allergic dermatitis, stomatitis, asthma, neuropathy, disturbances of the central nervous system, liver toxicity, and fertility disturbances (Leggat, 2003). The methacrylates (2-HEMA, TEGDMA and BIS-GMA) are not only strong irritants, but also notorious allergens. Numerous studies confirm the length promenade incidence of sensitization to methacrylates in dental professionals (Alanko, 2004, Goon, 2006, Prasad Hunasehally, 2012, Scott, 2004), as well as in patients undergoing dental treatment and exposed to resin-based materials (Gawkrodger, 2005, Tillberg, 2009).

Acrylic monomers often cross-react - that is, allergic sensitization induced by one acrylic compound extends to one or more other acrylic compounds. Therefore, sensitized individuals are often multi allergic and, accordingly, cannot be exposed to any of the compounds (Goon, 2006, Aalto-Korte, 2010, Kanerva, 2001a). Another important aspect is that product declarations of dental acrylic materials should show all acrylic compounds present in the products, even acrylic monomers/impurities with lower concentrations than 1%. This could help to select a product that the sensitized individual could be exposed to (Kanerva 2001b). Quite a few studies are available aiming to evaluate the incidence of cross-sensitization in students of dentistry and of dental technician school. The aim of the present study is to evaluate the incidence and to perform a comparative risk assessment of cross-sensitization to methacrylic monomers in different groups of individuals, exposed in dental practice.

MATERIALS AND METHODS

Participants

A total of 262 participants were included in a study which were divided into four main groups – 49 randomly chosen dental patients of different gender, age and occupations, the main inclusion criteria being the lack of occupational exposure to methacrylic monomers, 110 students of dental medicine, 38 students from Dental technician school, and 65 dental professionals who were occupationally exposed to methacrylic monomers. Data regarding age and gender characteristics are presented in Table 1. The study was granted by the Medical University – Sofia, Grant № 5-C/2013, and was approved the Medical Ethics Board at the Medical University of Sofia. All participants were informed about the purpose of the study and gave their written informed consent.

Skin Patch Testing

Skin patch testing with MMA, TEGDMA, ethyleneglycol dimethacrylate (EGDMA), BIS-GMA, 2-HEMA and tetrahydrofurfuril metacrylate (THFMA) was performed, according to the Jadassohn & Bloch classical methods for diagnosis of contact allergy, by placing the allergens (0.2%/pet, Chemotechnique Diagnostics) in IQ-Ultra hypoallergenic patches of Chemotechnique Diagnostics (IQ Chambers ®, Vellinge, Sweden). Obligatory condition was lack of anti-allergic medication before placing the patches and during the study. Patches with allergens were applied and stayed on the back of the tested subjects; reading of the test was carried out on day 2, several hours after removing of the patches, with control revision on day 3. Interpretation of reaction sites was based on the method recommended by the International Contact Dermatitis Research Group (ICDRG). Interpretation key based on recommendations by the ICDRG was applied (Table 2).

Statistical Methods

Available for cross-tabulation statistics were used: chi-square test, Fisher Exact Test for statistical significance, testing of the ratio of two probabilistic ones OR (Odds ratio). Values of $p<0.05$ were accepted as statistically significant.

RESULTS

Due to the feminization of many occupations in dental medicine, the gender distribution was not uniform, with predominance of women in all the studied groups and in the overall distribution. Nevertheless, no significant difference in the gender distribution was found ($\chi 2=6.29$, $p=0.98$). Concerning the mean age of the studied groups, logically, significant higher ($P = 0.002$) was the mean age of the groups of dental patients and the occupationally exposed dental professionals if compared with those of students (Table 1).

Table 1. General characteristics of the studied groups of individuals

Studied group	Age (years) (M±SD)	Gender		Total
		Women n (%)	Men n (%)	
Dental patients	40,89 ± 18,26	39 (79.5)	10 (20.5)	49
Students of dental medicine	22,44 ± 2,96	68 (61.8)	42 (38.2)	110
Students of dental technician school	23,95 ± 5,70	29 (74.3)	9 (25.7)	38
Dental professionals	39,56 ± 9,80	47 (72.3)	18 (27.7)	65
Total	39.9± 16.3	183 (69.8)	79 (30.2)	262

Table 2. Interpretation key of skin patch test results based on International Contact Dermatitis Research Group

Symbol	Meaning
(–)	Negative reaction
?	Doubtful reaction (faint macular. no infiltration, homogenous erythema)
+	Weak positive reaction (non-vesicular)
++	Strong positive reaction (oedematous or vesicular)
+++	Extreme positive reaction (ulcerative or bullous)
IR	Irritant reaction (discrete patchy erythema without infiltration)

Summary of the data concerning the incidence of cross-sensitization to the investigated methacrylic monomers are presented in Table 3. As shown in Table 3, highest was the incidence of sensitization to the investigated methacrylic monomers in the groups of dental patients and the students of dental medicine. In the group of dental patients, highest was the incidence of sensitization to BIS-GMA (positive skin patch tests were observed in 30.6% of the individuals). The between-groups statistical analysis revealed a significantly higher

Table 3. Incidence of sensitization to the methacrylic monomers in the studied groups

Studied group	Incidence of sensitization to: (% of sensitized individuals)					
	MMA %	TEGDMA %	EGDMA %	bis-GMA %	2-HEMA %	THFMA %
Dental professionals	10.8%	16.9%	12.3%	13.8%	16.9%	12.3%
Students of Dental medicine	26.4%*	33.6%*	28.2%*	30.0%*	29.1%*	28.2%*
Students of dental technician school	15.8%	18.4%	10.5%	10.5%	5.3%	5.3%
Dental patients	24.5%	26.5%	24.5%	30.6%*	24.5%*	28.8%*
Total	20.6%	25.9%	21.0%	23.3%	21.8%	21.0%

MMA – methyl methacrylate, **TEGDMA** - triethyleneglycol dimethacrylate, **EGDMA** - ethyleneglycol dimethacrylate, **bis-GMA** - 2,2-bis-[4-(2-hydroxy-3-methacrylo-xypropoxy)phenyl]-propane, **2-HEMA** - 2-hydroxy-ethyl methacrylate, **THFMA** - tetrahidrofurfuril metacrylate

Table 4. Incidence of cross-sensitization to METHACRYLATES (MMA+2-HEMA+THFMA) and to EGDMA, bis – GMA and TEGDMA in the studied groups

Studied group according to type of exposure and sensitization to:	SENSITIZATION TO *METHACRYLATES (MMA+2-HEMA+THFMA)*			
	Negative n (%)	Positive n (%)	Total	*p, (*p< 0.05); OR, 95%CI*
		EGDMA		
Dental patients	24 (96.0)	13 (54.2)	37	*p=0.001; OR=19.64,
	1 (4.0)	11 (45.8)	12	95% CI=2.29 – 168.48
Students of Dental medicine	38 (84.4)	41 (62.1)	79	*p=0.014; OR=3.18,
	7 (15.6)	24 (37.9)	31	95% CI=1.23 – 8.22
Students of dental technician school	27 (90.0)	7 (87.5)	34	*n.s.*
	3 (10.0)	1 (12.5)	4	
Dental professionals	43 (91.5)	14 (77.8)	57	*n.s.*
	4 (8.5)	4 (22.2)	8	
		bis – GMA		
Dental patients	21 (87.5)	14 (56.0)	35	*p=0.025; OR=4.32,
	3 (12.5)	14 (56.0)	14	CI=1.15 – 16.28
Students of Dental medicine	38 (86.4)	40 (60.6)	78	*p=0.006; OR=3.62,
	6 (13.6)	26 (39.4)	32	95% CI=1.41 – 9.31
Students of dental technician school	28 (93.3)	6 (75.0)	34	*n.s.*
	2 (6.7)	2 (25.0)	4	
Dental professionals	43 (91.5)	13 (72.2)	56	*p=0.048
	4 (8.5)	5 (27.8)	9	
		TEGDMA		
Dental patients	24 (96.0)	12 (50.0)	36	*p<0.001; OR=23.08,
	1 (4.0)	12 (50.0)	13	95% CI=2.70 – 197.57
Students of Dental medicine	38 (86.4)	36 (54.5)	74	*p=0.001; OR=4.64,
	6 (13.6)	30 (45.5)	33	95% CI=1.82 – 11.88
Students of dental technician school	26 (86.7)	5 (62.5)	31	*n.s.*
	4 (13.3)	3 (37.5)	7	
Dental professionals	40 (87.0)	13 (68.4)	53	*n.s.*
	6 (13.0)	6 (31.6)	12	

MMA – methyl methacrylate, **TEGDMA** - triethyleneglycol dimethacrylate, **EGDMA** - ethyleneglycol dimethacrylate, **bis-GMA** - 2,2-bis-[4-(2-hydroxy-3-methacrylo-xypropoxy)phenyl]-propane, **2-HEMA** - 2-hydroxy-ethyl methacrylate, **THFMA** - tetrahidrofurfuril metacrylate

incidence and OR for sensitization to BIS-GMA in the group of dental patients if compared with the group of dental professionals ($\chi2$=4.05, p=0.044; OR=0.39, 95% CI=0.16 – 0.99) and the students of dental technician school ($\chi2$=4.62, p=0.032; OR=0.28, 95% CI=0.09 – 0.94). On other hand, an increased incidence and OR for sensitization to BIS-GMA was observed in the group of students of dental medicine if compared with the groups of students of dental technician school ($\chi2$=5.48, p=0.019; OR=0.28, 95% CI=0.09 – 0.86) and the dental professionals ($\chi2$=5.317, p=0.012; OR=0.392, 95% CI=0.174 – 0.884). The most important allergen for the group of dental students was TEGDMA – 33.6% of the skin patch tested individuals had positive reaction, but significantly increased incidence and OR for sensitization was established

only if compared with the group of dental professionals ($\chi2$=5.40, p=0.020; OR=0.41, 95% CI=0.19 – 0.88). TEGDMA was the most important sensitizer for the group of students of dental technician school as well. High incidence and OR for sensitization to THFMA were established in the groups of dental patients (28.8% of the tested individuals manifested positive reaction) and dental students (28.2% of the studied subjects). For the patient's group the incidence and OR were significantly higher if compared with the group of students of dental technician school ($\chi2$=7.27, p=0.007; OR=0.15, 95% CI=0.03 – 0.69) and the one of dental professionals ($\chi2$=4.10, p=0.043; OR=0.38, 95% CI=0.14 – 0.99). Concerning the group of dental students, significantly higher were the incidence and OR for sensitization if compared with the groups of students of dental technician school ($\chi2$=8.31, p=0.004; OR=0.15, 95% CI=0.03 – 0.64) and the one of dental professionals ($\chi2$=5.44, p=0.020; OR=0.37, 95% CI=0.16 – 0.87). 2-HEMA ranked as the third allergen of importance for the group of dental students (Table 2), the incidence and OR of sensitization being significantly higher compared with the group of students of dental technician school ($\chi2$=8.79, p=0.003; OR=0.14, 95% CI=0.03 – 0.61). The latter is valid for the group of dental patients ($\chi2$=4.48, p=0.019; OR=0.18, 95% CI=0.04 – 0.86).

EGDMA was shown also to be an important sensitizing agent for dental students, the incidence and OR of sensitization being significantly higher in this group if compared with the ones of students of dental technician school ($\chi2$=4.67, p=0.031; OR=0.31, 95% CI=0.10 – 0.94) and of dental professionals ($\chi2$=5.66, p=0.017; OR=0.37, 95% CI=0.16 – 0.86). Concerning the sensitization rates to MMA, surprisingly, the only significant difference observed in the between-groups analysis was the higher incidence and OR in the group of students of dental medicine if compared with the one of dental professionals ($\chi2$=5.81, p=0.016; OR=0.35, 95% CI=0.14 – 0.84). Interestingly, the statistical analysis of gender distribution of the sensitization to the investigated methacrylic monomers demonstrated, with high significance, increased incidence and OR of sensitization to most of the tested methacrylic monomers (e.g. TREGDMA, EGDMA, BIS-GMA, 2-HEMA and tetrahydrofurfuryl methacrylat) among men from all the studied groups. Further, we compiled a new group – the one of individuals, sensitized to more than one of the following methacrylic monomers - MMA, 2-HEMA and THFMA and assess the manifestation of cross-sensitization with the other studied monomers. Results of the defined groups are presented in Table 4.

The between-groups statistical analysis revealed, with very high significance, increased incidence and OR of sensitization to more than one of the monomers MMA, 2-HEMA and THFMA among the students of dental medicine if compared with the dental professionals ($\chi2$=15.49, p<0.001; OR=0.27, 95% CI=0.14 – 0.53) and with the students of dental technician school ($\chi2$=16.28, p<0.001; OR=0.19, 95% CI=0.08 – 0.44). Also, a significantly increased were the incidence and OR for cross-sensitization in the control group if compared with students of dental technician school ($\chi2$=7.30, p=0.007; OR=0.28, 95% CI=0.11 – 0.72) and the dental professionals ($\chi2$=5.29, p=0,021; OR=0.41, 95% CI=0.19 – 0.88).

DISCUSSION

Nowadays, numerous (meth) acrylates have found applications in a variety of dental resin-based materials as well as in consumer products such as paints and adhesives, printing inks, artificial nails, medical devices - contact lenses, hearing aids, etc. (Sasseville, 2012). Concomitant occupational and consumer exposures are possible for dental professionals and students of dentistry. Due to the specificity and the chemical composition of the used materials dental technicians during their education and work are mostly exposed to MMA and to a less degree to dental composites. For dental professionals and students of dentistry the main source of exposure to methacrylic monomers are composite materials, adhesives, sealants, bonding cements, etc. Resin-based dental materials are not inert in the oral environment of dental patients, and may release numerous components, including methacrylic monomers. For dental patients everyday consumer's exposure is of importance as well (Van Landuyt, 2011). Assessment of possible manifestation of cross-sensitization to methacrylic monomers could be of great significance for choosing a proper material for treatment of sensitized dental patients. Early detection of cross-sensitization among dental students is beneficial for prevention of further occupational pathology and even permanent disability.

The present study includes a total of 262 subjects, divided into four groups, with predominance of women participating, but without significant difference in the gender distribution. Dental patients and dental students could outline these groups being at risk since highest sensitization incidence was found in these groups. Aiming to distinguish the importance of consumer/environmental and in dental practice exposures we performed a detailed between-group analysis of sensitization rates for each of the investigated methacrylic monomer. Surprising were the results concerning the incidence of sensitization to MMA. High rates were observed in the group of dental patients (mean age 40.89±18.26) suggesting the role of dental restorative materials for sensitization onset. Dental student self-reported that they don't use regularly proper protective devices while handling methacrylate-containing materials at the first years of their course of education. This could be a possible explanation for the increased sensitization incidence among them. The statement about non-observance of good dental work practice among dental students seems to be supported by the established high prevalence of cross-sensitisation to more than one of the following methacrylates – MMA, 2-HEMA and THFMA and/or to EGDMA, BIS – GMA and TEGDMA in this group.

Among the groups of dental patients and of students of dentistry highest was the incidence of sensitization to bis-GMA. We could suggest that the main sources of sensitization are composite restorations. Nevertheless, the significantly increased incidence and OR for cross-sensitisation to bis-GMA and/or to MMA, 2-HEMA and THFMA suggest a possible role of other methacrylate-based consumer products. Due to the related to their age characteristics of dental status, students of dentistry are probably exposed mainly in the course of their education, when handling composite materials without proper protection and use of "no-touch" technique. Basing on the findings on lower incidence of sensitization among dental professionals we suggest that they better

educated and trained in good working practices application. 2-Hydroxyethyl methacrylate (2-HEMA) is used in UV-inks, adhesives, lacquers, artificial nails and many other consumer products. It was one of the first materials to be successfully used in the manufacture of flexible contact lenses (Ratner, 2004). Nowadays, it was shown that sensitization to 2-HEMA led to strong cross-reactions to all other methacrylates. According to our results, the groups of dental patients and of dental students to are most vulnerable. This suggests the significant role of both dental materials and consumer products. Triethylene glycol dimethacrylate is used as cross-linking agent for adhesives and dental restorative materials. In our study, TREGDMA could be outlined as the methacrylic monomer with highest sensitizing capacity for dental students and for those from dental technician school, as well as for dental patients. The significantly higher incidence and OR of cross-sensitization in dental patients and students of dentistry again suggest the role of dental treatment and handling with composite restorative materials without protective wear.

Ethyleneglycol dimethacrylate is used, in addition to dental polymers, in industrial and consumer products as photopolymer printing plates, paper processing aids, adhesives, contact lenses, artificial fingernails, conductive gels for medical use, leather finishing, and moisture barriers in packaging (BASF, 2013). In our study, EGDMA was of significant importance as sensitizing agent for dental students. Again a role of unsafe handling during the educational exposure could be suggested. Tetrahydrofurfuryl methacrylate is used in dental materials such as crown and bridge products, also in artificial nails, dental resins, electrical cable coatings, contact lenses, and in curing nitrile rubber (Chemotechnique diagnostics, 2013). The groups of dental patients and dental students again are outlined as most vulnerable, and it is difficult to distinguish clearly the role of consumer and in dental practice exposures for sensitization onset. According to our results, the most common allergens in methacrylic dental professionals were 2-HEMA and TEGDMA, confirming those reported by (Aalto-Korte, 2010).

No evidence to serve as a benchmark concerning the main methacrylic allergens for students of dentistry and from the dental technician school was found in the available literature. According to the results of our study, for students of dentistry main sensitizers are TEGDMA, bis-GMA and 2-HEMA. According to the authors cited above, the most important allergens for dental technicians are MMA and EGDMA. Our results indicate, somewhat surprisingly, TEGDMA, followed by MMA as most frequent sensitizers for the students from dental technician school. Regarding the control group, we found alarming high incidence of sensitization (over 24%) to all methacrylic monomers, "leaders" being bis-GMA and THFDMA. We assume a significant role of therapy with restorative composite materials for the occurrence of sensitization to methacrylic monomers. Students of dentistry and the control group could be considered at risk of cross-sensitization to methacrylic monomers.

Conclusion

The results from our study indicate high incidence of sensitization to methacrylic monomers in dental practise, with cross-sensitization clearly manifested. Students of dentistry and dental patients could be outlined as groups at risk, suggesting the role of exposures to methacrylic monomers both as an ingredient of dental restorative materials and of consumer products. New, more intensive health and safety promotion interventions during the course of education of dentistry are recommended.

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